UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/869,554	06/28/2001	Anna Edman Orlefors	HO-P0221US0	4792

26271 7590 07/06/2005

FULBRIGHT & JAWORSKI, LLP
1301 MCKINNEY
SUITE 5100
HOUSTON, TX 77010-3095

EXAMINER	
SAKELARIS, SALLY A	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 07/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/869,554	ORLEFORS ET AL.	
	Examiner	Art Unit	
	Sally A. Sakelaris	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,4,6,12,16 and 19-73* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,4,6,12,16 and 19-73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/2/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 2, 4, 19, 41, 46, 47, 51, 55, and 56 have been amended, claims 1, 3, 5, 7-11, 13-15, and 17-18, have been canceled, and claims 57-72 have been added. Claims 2, 4, 6, 12, 16, and 19-73 are now pending. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. All rejections not reiterated herein are hereby withdrawn as necessitated by applicant's amendments to the claims. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This action is FINAL.

THE FOLLOWING ARE NEW GROUNDS OF REJECTION NECESSITATED BY APPLICANT'S AMENDMENTS TO THE CLAIMS

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1. Claims 2, 20, 21, 32, 35, 36, 42 and new claims 57 and 58 are rejected under 35 U.S.C. 102(b) as being unpatentable over Ronaghi et al.(Anal. Biochemistry, 1996).

Interpreting claim 2's recitation of a "microfluidic device" to mean any device which is suitable to operate with liquids on a microliter scale, Ronaghi et al. teaches the methods of such a device(for example the capillary embodiment on page 88 bottom right).

With respect to claim 2, Ronaghi et al. teach a method of identifying the sequence of a portion of sample DNA comprising the sequential steps of:

(i) forming immobilized DNA comprising of one strand of sample DNA and one strand of primer DNA on two or more reaction areas in a microchannel structure of a microfluidic device(Pg. 85, bottom right). Incubating the nucleic acid sample with about 0.8 pmol primer, DNA polymerase, and a deoxynucleotide triphosphate(Page 88, Fig. 5).

(ii) adding reagents including deoxynucleotide or deoxynucleotide analogue and DNA polymerase and moving said reagents within said microchannel structure to each of said one or more reaction areas so that extension of primer occurs as a result from complementarity of the added deoxynucleotide or deoxynucleotide analogue with the strand of sample DNA that is part of the immobilized double stranded DNA(Page 85- 86)

(iii) detecting whether or not the deoxynucleotide or deoxynucleotide analogue added in step (ii) is added to the primer DNA in said one or more reaction areas;(Page 86).

(iv) removing excess of said deoxynucleotide or deoxynucleotide analogue from said from one or more reaction areas; is taught throughout the Ronaghi reference in their teachings in Figure 1 and later on page 87 as they wash the beads on which the deoxynucleotides are immobilized, the reference further teaches the loss of these excess, unincorporated, deoxynucleotides following the wash steps on page 87.

(v) repeating sequentially steps (ii)-(iv) with different deoxynucleotides or deoxynucleotide analogues is taught by Ronaghi in Figure 1 and in the text of Page 87 in their teaching that "the sequencing procedures were repeated several times".

(vi) identifying said sequence from the results of the above previous steps is obviously then taught in the reference's sequencing previously alluded to in (v) and furthermore that "the

obtained sequence was confirmed by semiautomated solid-phase Sanger sequencing"(Pg. 87, see figure 5).

With regard to applicant's newly added limitation to claim 2, requiring the steps to take place sequentially, such a limitation, after further review, is seen as being taught by Ronaghi. Specifically the reference's FIG.1 depicts such a sequential method consisting of the addition of dXTPs, detection, and then washing, followed by the repetition of the cycle again.

With regard to applicant's second newly added limitation to the claim requiring sample DNA and one strand of primer DNA on two or more reaction areas in a microchannel structure is also seen as being taught by Ronaghi. Specifically, Ronaghi teach on page 85 left hand side that the "oligonucleotide E3PN and the above described PCR product were used as templates for real-time DNA sequencing and the oligonucleotide E3PN was immobilized onto streptavidin-coated super paramagnetic beads". Thus the oligo was immobilized to two or more reaction areas since the entire bead was used, and not only a single oligo was immobilized on a single bead, many on multiple locations were affixed. Also, it is important to note that the office's interpretation of reaction area is due in part to the fact that the beads(presently viewed as "reaction areas"), are incubated with T7 DNA polymerase, and as a result subjected to an extension reaction of the polymerase.

With regard to claim 20, Ronaghi et al. teaches the above method wherein the detecting step (iii) measures the release of pyrophosphate(Page 85).

With regard to claim 21, Ronaghi et al further teach the method wherein the pyrophosphate release is detected by light emitted from a luciferin luciferase reaction(Fig. 1, Pg. 85).

With regard to new claim 32, Ronaghi et al. further teaches the method of claim 2 wherein step (iv) is washing said one or more reaction areas to remove excess of said deoxynucleotide or deoxynucleotide analogue in their teaching on the left side of page 85 of "washing of the immobilized DNA fragments between each nucleotide addition was performed"(Ronaghi pg. 85). Additionally the reference teaches in the abstract that the "parallel processing of many samples in an automated manner is discussed".

With regard to claims 35 and 36, the reference anticipates the limitations of the method of claim 2 and claim 35 wherein the amount of DNA sample is in the range of about 1 femtomole to about 200 pmole and also about 0.1 pmol to about 200pmol in their teaching on page 85 of "one picomole of the immobilized DNA fragment" being used in the sequencing reaction.

With regard to claim 42, the reference anticipates the limitations of the method of claim 2 and claim 42 wherein said immobilized DNA is immobilized to a bead in their teaching on page 85 of "the biotinylated PCR products were immobilized onto streptavidin-coated super paramagnetic beads Dynabeads M280-Streptavidin or M450-streptavidin"(left hand side), which were later used for sequencing.

With regard to new claims 57 and 58, the microchannel structure is associated with a common application area wherein the microchannel structure is being interpreted as being a capillary tube or a reaction tube, and further wherein the common application area is being interpreted as an area where reagents are applied in common. In this case, such a limitation is met by either the opening of the capillary tube or the opening of the reaction tube, both meeting the limitations of the claim as different dNTPs are added successively through these two common application areas and both meeting the limitation of claim 58 of being annular in shape.

Response to Arguments:

Applicant's arguments filed 4/7/2005 have been fully considered but they are not persuasive. While applicant argues that nowhere Ronaghi's teaching is there a recitation of two or more reaction areas, applicant is pointed to the office's interpretation of the beads being coated in two or more reaction areas by immobilized oligonucleotides located in for example the capillary tube of Ronaghi, that is a microchannel structure of a device that is moving liquids on a microliter scale. For the record and for clarity purposes, Page 85 on the left hand side teaches the "oligonucleotide E3PN and the above described PCR product were used as templates for real-time DNA sequencing and the oligonucleotide E3PN was immobilized onto streptavidin-coated super paramagnetic beads". Thus the oligo was immobilized to two or more reaction areas since the entire bead was used, and not only a single oligo was immobilized on a single bead, many on multiple locations were affixed. Also, it is important to note that the office's interpretation of reaction area is due in part to the fact that the beads/presently applied reaction areas, are incubated with T7 DNA polymerase, and as a result subjected to an extension reaction of the polymerase. In addition the examiner is nterpreting claim 2's recitation of a "microfluidic device" to mean any device which is suitable to operate with liquids on a microliter scale, Ronaghi et al. teaches the methods of such a device(for example the capillary embodiment on page 88 bottom right).

Applicant in reminded that limitations of the specification cannot be read into the claims and the claims have to be examined as broadly as they could be read. Limitations in applicant's arguments, specification etc cannot be read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Furthermore, without a requirement in the claims for the

exact device that is used in this method that applicant is arguing, the art will be applied as broadly as the claims are written. The courts have stated that claims must be given their broadest reasonable interpretation consistent with the specification *In re Morris*, 127 F.3d 1048, 1054-55, 44 USPQ2d 1023, 1027-28 (Fed. Cir. 1997); *In re Prater*,415 F.2d 1393, 1404-05, 162 USPQ 541, 550-551 (CCPA 1969); and *In re Zletz*, 893 F.2d 319, 321-22, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989) (see MPEP 2111). Applicant is pointed to page 88 of the Ronaghi reference and their teaching of their immobilization of the DNA template in a capillary and their further characterization of such a system as "a flow system, with small volumes, high speed", which meets applicant's own standard of a characteristic of a microfluidic device.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 2, 4, 6, 12, 16, 19-31, 33, 34, 37-40, 41-56, and new claims 57-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ronaghi et al.(Anal. Biochemistry, 1996) in view of Mian et al.(US Patent 6,319,469 B1).

Interpreting claim 2's recitation of a "microfluidic device" to mean any device which is suitable to operate with liquids on a microliter scale, Ronaghi et al. teaches the methods of such a device(for example the capillary embodiment on page 88 bottom right).

With respect to claim 2, Ronaghi et al. teach a method of identifying the sequence of a portion of sample DNA comprising the sequential steps of:

(i) forming immobilized DNA comprising of one strand of sample DNA and one strand of primer DNA on one or more reaction areas in a microchannel structure of a microfluidic device(Pg. 85, bottom right). Incubating the nucleic acid sample with about 0.8 pmol primer, DNA polymerase, and a deoxynucleotide triphosphate(Page 88, Fig. 5).

(ii) adding reagents including deoxynucleotide or deoxynucleotide analogue and DNA polymerase and moving said reagents within said microchannel structure to each of said one or more reaction areas so that extension of primer occurs as a result from complementarity of the added deoxynucleotide or deoxynucleotide analogue with the strand of sample DNA that is part of the immobilized double stranded DNA(Page 85- 86)

(iii) detecting whether or not the deoxynucleotide or deoxynucleotide analogue added in step (ii) is added to the primer DNA in said one or more reaction areas;(Page 86).

(iv) removing excess of said deoxynucleotide or deoxynucleotide analogue from said from one or more reaction areas; is taught throughout the Ronaghi reference in their teachings in Figure 1 and later on page 87 as they wash the beads on which the deoxynucleotides are immobilized, the reference further teaches the loss of these excess, unincorporated, deoxynucleotides following the wash steps on page 87.

(v) repeating sequentially steps (ii)-(iv) with different deoxynucleotides or deoxynucleotide analogues is taught by Ronaghi in Figure 1 and in the text of Page 87 in their teaching that "the sequencing procedures were repeated several times".

(vi) identifying said sequence from the results of the above previous steps is obviously then taught in the reference's sequencing previously alluded to in (v) and furthermore that "the obtained sequence was confirmed by semiautomated solid-phase Sanger sequencing"(Pg. 87, see figure 5).

With regard to applicant's newly added limitation to claim 2, requiring the steps to take place sequentially, such a limitation, after further review, is seen as being taught by Ronaghi. Specifically the reference's FIG.1 depicts such a sequential method consisting of the addition of dXTPs, detection, and then washing, followed by the repetition of the cycle again.

With regard to claim 20, and new claims 68 and 70, Ronaghi et al. teaches the above method wherein the detecting step (iii) measures the release of pyrophosphate(Page 85).

With regard to claim 21, and new claims 69 and 71 Ronaghi et al further teach the method wherein the pyrophosphate release is detected by light emitted from a luciferin luciferase reaction(Fig. 1, Pg. 85).

With regard to claims 32, 33, and 34 Ronaghi et al. further teaches the method of claim 2 wherein step (iv), claim 4 wherein step (vi), and claim 19, wherein step (vii) is washing one or more reaction areas to remove excess of said deoxynucleotide or deoxynucleotide analogue in their teaching on the left side of page 85 of "washing of the immobilized DNA fragments between each nucleotide addition was performed"(Ronaghi pg. 85). Additionally the reference teaches in the abstract that the "parallel processing of many samples in an automated manner is discussed".

With regard to claims 35-40 the reference anticipates the limitations of the method of claim 2, 35, 4, 19, 37, and 39 wherein the amount of DNA sample is in the range of about 1

femtomole to about 200 pmole and also about 0.1 pmol to about 200pmol in their teaching on page 85 of "one picomole of the immobilized DNA fragment" being used in the sequencing reaction.

With regard to claims 42, 43, 50 and 52 the reference anticipates the limitations of the method of claim 2 and claim 42 wherein said immobilized DNA is immobilized to a bead in their teaching on page 85 of "the biotinylated PCR products were immobilized onto streptavidin-coated super paramagnetic beads Dynabeads M280-Streptavidin or M450-streptavidin"(left hand side), which were later used for sequencing.

With regard to new claims 57-67, the microchannel structure is associated with a common application area wherein the microchannel structure is being interpreted as being a capillary tube or a reaction tube, and further wherein the common application area is being interpreted as an area where reagents are applied in common. In this case, such a limitation is met by either the opening of the capillary tube or the opening of the reaction tube, both meeting the limitations of the claim as different dNTPs are added successively through these two common application areas and both meeting the limitation of claim 58 of being annular in shape.

With regard to claim 72 and applicant's newly added limitation to the claim requiring sample DNA and one strand of primer DNA on two or more reaction areas in a microchannel structure is also seen as being taught by Ronaghi. Specifically, Ronaghi teach on page 85 left hand side that the "oligonucleotide E3PN and the above described PCR product were used as templates for real-time DNA sequencing and the oligonucleotide E3PN was immobilized onto streptavidin-coated super paramagnetic beads". Thus the oligo was immobilized to two or more reaction areas since the entire bead was used, and not only a single oligo was immobilized on a

single bead, many on multiple locations were affixed. Also, it is important to note that the office's interpretation of reaction area is due in part to the fact that the beads(presently viewed as "reaction areas"), are incubated with T7 DNA polymerase, and as a result subjected to an extension reaction of the polymerase.

But, with respect to Claims 4, 6, 12, 16, 19, 22-31, 41, 43-56 and new claims 59-72 Ronaghi et al. does not teach a method for identifying the sequence of a portion of sample DNA wherein the steps are performed in a microfluidic device that is a disk and the fluids are moved(claims 4, 12, 16, and 19) by centripetal force, such as that which is referred to on page 5, line 32 of the current specification. Additionally, they do not teach the microfluidic device comprising microchannel structures with a common application area and a reaction chamber in each of said microchannel structures. Furthermore, Ronaghi et al. does not teach labeling the deoxynucleotide, deoxynucleotide analogue, or dideoxynucleotide that is added in the method.

However, Mian et al. (US Patent 6,319,469 B1) teach performing the previously taught methods of Ronaghi inside another type of microfluidic device. Mian et al. teach performing the steps of adding sample DNA on a reaction area in a microfluidic device(see Col. 49 lines 1-4), attaching or hybridizing single stranded DNA, and plainly adding sample DNA to a predetermined area on a microfluidic device that is a disc and whose fluids can be moved to various chambers(Col. 49 lines 2-19). Furthermore, the Mian et al. reference adds teachings of a disc-shaped, microfluidic device that causes fluid movement through the use of centripetal force(Col. 3 lines 5-25). The reference even further teaches that such methods and apparatus are advantageous as they fill the need in the art for a "simple, flexible, reliable, rapid, and economical microanalytic and microsynthetic reaction platform for performing biological,

biochemical, and chemical analyses and syntheses that can move nanoliter to microliter amounts of fluids"(Col. 3 lines 5-10). The reference provides that the invention also advantageously combines "wet" chemistry capabilities with information processing, storing and manipulating ability. The addition of the disc-shaped microfluidic device that exploits centripetal force, to this method for sequence identification, conferred the ability to properly mix reaction components, remove reaction side products, and isolate desired reaction products and intermediates.(Col 3, lines 5-25)(Col 48, line 67) Furthermore, Mian et al. add the teaching of forming DNA to a "microchannel structure" within the microfluidic device. The reference teaches that; the unique disc shape and ability to move nanoliter to microliter amounts of fluid, including reagents and reactants, at rapid rates to effect the proper mixing of reaction components through the use of microchannel structures and centripetal force, provides a remedy for the many deficiencies of the status quo. The use of microchannels, functioning to separate micro-amounts of fluid reagents, and centripetal force, to move fluids into and out of reaction chambers, facilitates high-throughput analysis for both genome sequencing and routine clinical applications "that are sophisticated(for professional, eg hospital, use), easy to use(for consumer eg at-home monitoring, uses), and portable (for field environmental testing, use)" (Col. 3 lines 19-22). In addition, with regard to the new limitations requiring multiple reaction areas containing immobilized DNA(i.e. new claims 45, 46, 48, 49, 54, and 56) Mian et al. teach "disks comprising a multiplicity of these synthetic arrays, permitting simultaneous synthesis of a plurality of dideoxynucleotide-terminated oligonucleotides"(Col. 49 lines 31-34). Furthermore, with regard to the new limitations requiring that the immobilized DNA is formed outside the microfluidic structure(i.e. claims 44 and 53) Mian et al. teaches in Col.42 lines 64-67 for example, that "in the

practice of the method of the invention, the immobilized, labeled duplex is placed on the disk and subjected to a flow stream of a buffered solution contained on the disk"(Col. 42) also in Col. 43 lines 26-33 the reference teaches immobilization of DNA either before or after the DNA is on the disk.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have conducted the method of Ronaghi et al. in view of the methods of Mian et al. by incorporating a disc-shaped microfluidic device with microchannels and caused fluid flow through the use of centripetal force in order to have achieved the expected benefit of providing a method that could be used for the automation of larger sequencing projects and for the provision of a "high-throughput system."

With respect to Claims 6, 22, 25, 26, and 29-31 and the limitation of a fluorescently labeled dideoxynucleotide, Mian teaches a detection step that involves a labeled terminator (Col 49, lines 5-10). Mian et al. teach a method wherein the detection step comprises the DNA being transferred into a mixing chamber containing terminator solution by spinning the disk(Col. 47 lines 15, 28, 39 for example). Terminator solution typically comprises 100nl of a solution containing 5 picomoles of each deoxynucleotide and 0.5 picomoles of one dideoxynucleotide covalently linked to a fluorescent label. The set of dideoxynucleotide-terminated DNA fragments comprising the reaction mixture is then separated by capillary electrophoresis and the sequence of the fragments determined by laser-induced fluorescence detection. The reference further teaches that this mode of detection ie, discs comprising a multiplicity of these synthetic arrays with fluorescent labels, permits the simultaneous synthesis of a plurality of dideoxynucleotide-terminated oligonucleotides and therefore applicable in high throughput

analysis of sequencing data or clinical approaches. Mian et al. teaches the use of a terminator solution containing a dideoxynucleotide covalently-linked to a fluorescent label in Example 7, Col. 49. In addition, Mian et al. teach, in addition to the aforementioned, fluorescently labeled dideoxynucleotide of Example 7, Example 3 which includes the incorporation of fluorescently labeled DNA to one or more reaction areas so that extension of primer occurs as a result from complementarity of the added dideoxynucleotides with the strand of sample DNA that is part of the immobilized double stranded DNA.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have conducted the method of Ronaghi et al. in view of the methods of Mian et al. and to have added a labeled terminator and fluorescently labeled dideoxynucleotides, in order to have achieved the benefit of providing a method that, would permit the simultaneous synthesis of a plurality of fluorescently labeled dideoxynucleotide-terminated oligonucleotides and therefore applicable in high throughput analysis of sequencing data or clinical approaches.

Response to Arguments:

Applicant's arguments filed 4/7/2005 have been fully considered but they are not persuasive. Applicant first reminds the examiner that in their interview conducted on February 16, 2005, "the applicants indicated that the sequencing methods of Mian et al. were not similar to the ones of Ronaghi et al., in fact the sequencing methods taught by Mian et al. are Sanger sequencing as indicated in Example 7". However, the Mian et al. reference is not relied upon for teaching the exact limitations of sequencing currently being recited in the claims. The Ronaghi reference teaches the sequential order now required in the claims and practicing this method in the centripetally accelerated device of Mian et al. would have been obvious to one of ordinary

skill at the time the invention was made. The specific references to the Ronaghi reference are made in the above revised rejection. In addition, the examiner maintains that the legal standard for "reasonable expectation of success" is provided by caselaw and is summarized in MPEP 2144.08, which notes "obviousness does not require absolute predictability, only a reasonable expectation of success; i.e., a reasonable expectation of obtaining similar properties. See , e.g. , In re O'Farrell , 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988)." In this factual case, there is express suggestion in the prior art that sequencing can be performed by many art-recognized methods. There is further evidence as shown in Ronaghi et al. that the method including detection of pyrophosphate release lends itself to the "possibility for parallel processing of many samples in an automated manner". This is sufficient for a reasonable expectation of success considering the Mian et al reference provides a parallel processing, automated, microfluidic device. The MPEP cites In re O'Farrell, which notes regarding "obvious to try" at page 1682, that,

> "In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. E.g ., In re Geiger , 815 F.2d at 688, 2 USPQ2d at 1278; Novo Industri A/S v. Travenol Laboratories, Inc ., 677 F.2d 1202, 1208, 215 USPQ 412, 417 (7th Cir. 1982); In re Yates , 663 F.2d 1054, 1057, 211 USPQ 1149, 1151 (CCPA 1981); In re Antonie , 559 F.2d at 621, 195 USPQ at 8-9. In others, what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it. In re Dow Chemical Co ., 837 F.2d, 469, 473, 5 USPQ2d

1529, 1532 (Fed. Cir. 1985); Hybritech, Inc. v. Monoclonal Antibodies, Inc ., 802 F.2d 1367, 1380, 231 USPQ 81, 90-91 (Fed. Cir. 1 986), cert. denied , 107 S.Ct. 1606 (1987); In re Tomlinson ; 363 F.2d 928, 931, 150 USPQ 623, 626 (CCPA 1966).

The court in O'Farrell then, affirming the rejection, notes "Neither of these situations applies here." For the instant case, it is clear that neither situations applies here either. This is not a situation where the prior art suggests varying a variety of parameters, since the prior art directly points to real time sequencing being performed in a microfluidic device in both the Ronaghi et al. reference and the Mian et al reference. This is also not a situation where only general guidance was given. The prior art provides specific guidance directing real time sequencing in a microfluidic device. It should further be noted that the new, independent claims as written do not require a particular method of sequencing to be used(i.e. do not require pyrosequencing.) and as a result the claims can be read broadly as long as the required elements of including a DNA polymerase and deoxynucleotide or deoxynucleotide analogue are met, which they are by both references.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sally A. Sakelaris whose telephone number is 571-272-0748. The examiner can normally be reached on M-Fri, 9-6:30 1st Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on 571-272-0745. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sally Sakelaris

6/21/2005

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600